## Role of Randomized Controlled Trials in Chronic Disease Population Research

- In therapeutic research RCT's have provided the scientific standard for some decades.
- The need for, and role of, RCT's in chronic disease population research (research aimed at identifying preventive treatments or interventions or public health recommendations) is somewhat controversial, primarily because of cost and logistical challenges associated with RCT's in this area.

## Role of Randomized Controlled Trials in Chronic Disease Population Research

In this talk….

- Primary prevention of cancer and other chronic diseases – a status report
- Some surprises from randomized controlled trials
- Sources of primary prevention hypotheses / interventions
- Infrastructure development needs
- But first… **what could we all have been doing this week, rather than sitting in a lecture hall…**


## Primary Prevention of Cancer

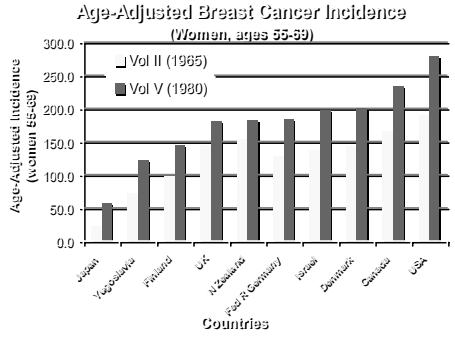
- **Known important causative agent**
  - Cigarette smoke -- lung, oral, esophageal, bladder, kidney, …
  - Hepatitis B virus -- liver
  - Human papilloma virus -- cervical
  - H pylori -- stomach cancer
- Research to find ways to reduce exposure and to change the behavior of individuals and groups
- Primary care physician counseling; regulatory approaches to exposure reduction

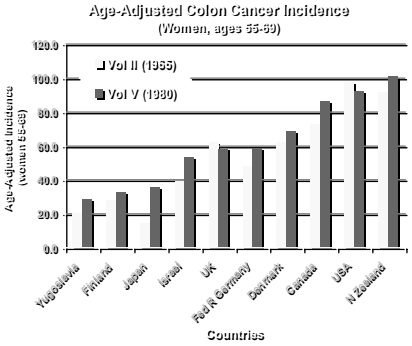
## Primary Prevention of Cancer (continued)

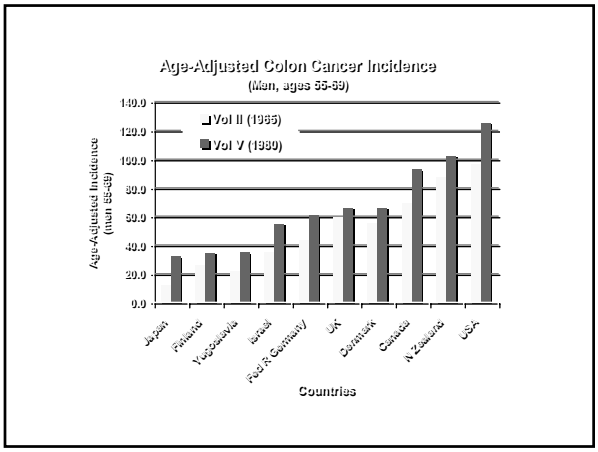
- **Etiology largely unknown, but incidence rates high in Western countries.**
  - Breast, colorectal, prostate, ovary (as well as some of the cancers previously mentioned)
- Research agenda toward reducing the risk of these cancers, and improving overall health?
- Role of randomized controlled trials

## Potential for Breast, Colon, Ovary, Prostate Cancer Prevention

- ⑤International variations in cancer incidence rates
- ⑤Time trends within countries in cancer incidence rates
- ⑤Cancer incidence rates among migrant populations




Age-Adjusted Colon Cancer Incidence
(Men, ages 55-59)
Vol II (1965)
Vol V (1980)
Age-Adjusted Incidence
(men 55-59)
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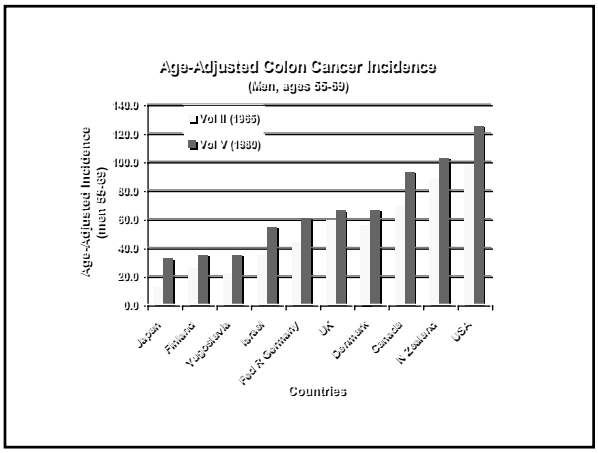
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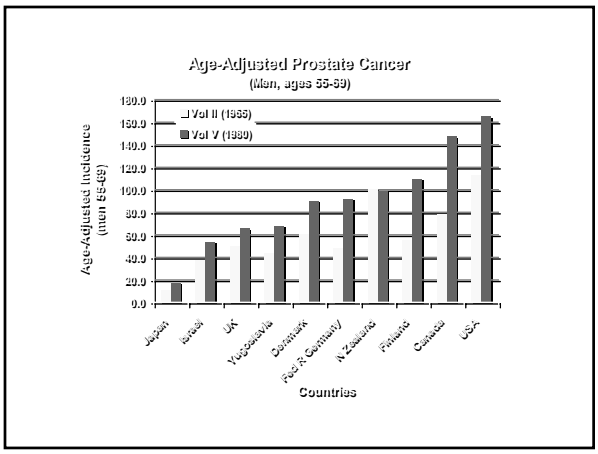

Age-Adjusted Prostate Cancer
(Men, ages 55-59)
Vol II (1965)
Vol V (1980)
Age-Adjusted Incidence
(men 55-59)
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
Japan
Israel
UK
Yugoslavia
Denmark
Fed R Germany
N Zealand
Finland
Canada
USA
Countries

## Age-Adjusted Cancer Incidence Ratios for Japanese in the United States versus Japanese in Japan

| Females | | | Males | |
|---|---|---|---|---|
| **Breast** | **Colon** | **Ovarian** | **Colon** | **Prostate** |
| 3.5 | 3.2 | 2.9 | 3.5 | 5.7 |

(Tominaga, 1985)

## Breast Cancer Relative Risk among Asian migrants to the USA, as a function of years in the West

| | Always lived in West | Years lived in the West | | | | |
|---|---|---|---|---|---|---|
| | | ≥22 | 15-21 | 8-14 | 5-7 | 2-4 |
| RR | 1.0 | 0.59 | 0.66 | 0.72 | 0.40 | 0.32 |
| 95% CI | | (.39,.91) | (.44,.97) | (.49,1.1) | (.24,.67) | (.18,.57) |

*(Ziegler et al, 1993, JNCI, 1819-27)*

## Associations are fine, but are there RCT's showing that the risks of these major cancers can be reduced?

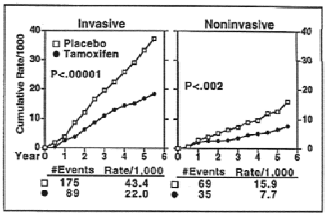
- **Breast cancer**
  - tamoxifen (Fisher et al, 1998, JNCI)
  - raloxifene (Cummings et al, 1999, JAMA)
- **Colorectal adenoma**
  - calcium (Baron et al, 1999, NEJM)
  - aspirin (Baron et al, 2003, NEJM)
- **Colorectal cancer**
  - combined hormone therapy (WHI, 2002, JAMA)

*Also on-going RCT's:*

- Prostate cancer -- finasteride, selenium, Vitamin E (SWOG)
- Breast and colorectal cancer -- lowfat eating pattern, calcium and Vitamin D (WHI)
- Epithelial cancers -- Vitamin C, E, multivitamins (Harvard)

**Any commonality among interventions?**

## Breast Cancer Rates




- Cumulative rates of invasive and noninvasive breast cancers occurring in participants receiving placebo or tamoxifen. The P values are two-sided.

*(Fisher et al, 1998, JNCI, p. 1371)*

## Colorectal Cancer Combined Hormone Therapy

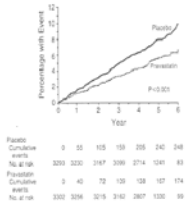
| Placebo (8102) | Estrogen + Progestin (8506) | H.R. (nominal 95% CI) |
|---|---|---|
| 67 | 45 | 0.63 (0.43,0.92) |

*(WHI, JAMA, 288, 321-333)*

## What about primary prevention of other major chronic diseases?

- Coronary heart disease?
  - lipids and blood pressure as important markers of risk (also markers of inflammation and thrombosis)
  - antihypertensive medications
  - aspirin / NSAID's
  - lipid lowering drugs, especially statin family drugs (e.g., Shepherd et al, 1995, NEJM)
- Fractures?
  - alendronate (Cummings et al, 1998, JAMA)
  - calcium and Vitamin D (Chapuy et al, 1994, BMJ)
- Diabetes?
  - metformin and lifestyle in Diabetes Prevention Program (DPP Research Group, 2002, NEJM)

## Coronary Heart Disease




Kaplan-Meier analysis of the time to a definite non-fatal Myocardial Infarction or Death from CHD. According to Treatment Group.

*(Shepherd et al, 1995, NEJM, p. 1301)*

## Fractures

**Alendronate** *(Cummings et al, 1998, JAMA, p. 2077)*
(T score > 2.5)

| ***Clinical Fractures*** | | | ***Vertebrae Fractures*** | | |
|---|---|---|---|---|---|
| Placebo(812) | Active (819) | H.R. (95% CI) | Placebo (812) | Active (819) | H.R. (95% CI) |
| 159 | 107 | 0.64 (0.50,0.82) | 44 | 22 | 0.50 (0.31,0.82) |

**Cholecalciferol and calcium** *(Chapuy et al, 1994, BMJ, p. 1081)*

| ***Clinical Fractures*** | | | ***Hip Fractures*** | | |
|---|---|---|---|---|---|
| Placebo (1127) | Active (1176) | P-value | Placebo (1127) | Active (1176) | P-value |
| 308 | 255 | < 0.02 | 178 | 137 | < 0.02 |

## Diabetes Prevention Program Research Group

3,234 nondiabetic persons with elevated glucose randomized to placebo, metformin (850mg twice daily) or lifestyle modification (7% weight loss, 150 minutes/wk of moderate physical activity). Stopped early after average 2.8 years of follow-up.

**Reduction in Incidence (%) of (Type II) Diabetes *(95% CI)***

| **Lifestyle vs. Placebo** | **Metformin vs. Placebo** | **Lifestyle vs. Metformin** |
|---|---|---|
| 58 (48,66) | 30 (17,43) | 39 (24,51) |

*(2002, NEJM, p. 393)*

## Summary / Issues

- For major cancers, of largely unknown etiology, modifiable 'lifestyle' factors are likely quite important (diet, physical activity, and energy balance, over lifespan). We are experiencing an obesity epidemic!
- Evidence that the risk for these cancers and a number of other major chronic diseases can be importantly reduced with just a few years of preventive intervention, even at advanced ages.
- Most intervention trials to date have focused on chemopreventive / pharmaceutical interventions.
- These trials typically target a particular disease and often have limited ability to assess overall benefits versus risks (the ultimate priority when intervening on ostensibly healthy persons).

## Some surprises in RCT's large enough to examine benefits versus risk…

- Beta carotene and lung cancer, CHD, and all cause mortality
- Combined hormone therapy, CHD, breast cancer and overall risks and benefits

## Beta Carotene Supplementation and Cancer, Coronary Heart Disease,and All-Cause Mortality

- Many observational studies indicate that persons self-reporting a relatively large consumption of foods rich in beta carotene (and other carotenoids) have a lower risk of cancer at several sites. Observational studies are particularly consistent for lung cancer (Ziegler et al, 1996, Cancer Causes and Control)
- At least 10 prospective studies reporting higher risk of lung cancer, heart disease, other cancer or all-cause mortality among persons having relatively low blood levels of beta carotene, e.g., RR=0.62 (0.44,0.87) for total mortality over 8.2 years average follow-up for persons having BC blood concentration in highest versus lowest quartile (Greenberg et al, 1996, JAMA)

## Intervention Trials of Beta Carotene Supplementation

Alpha Tocopherol,
Beta Carotene Cancer Prevention Study Group

- 29,133 male smokers 50-69 years of age
- 20mg/day beta carotene, 5-8 years follow-up
- Lung cancer RR=1.18 (1.03,1.36), 876 cases
- No significant difference for other cancers
- Total mortality RR=1.08 (1.01,1.16)

*(NEJM, 1994)*

## Carotene and Retinol Efficacy Trial

- 18,314 smokers, former smokers, and asbestos exposed persons
- 30mg BC plus 25000 IU retinol/day
- Trial stopped early after 4 years average follow-up
- Lung cancer RR=1.28 (1.04,1.57), 388 cases
- No significant difference for other cancers
- Cardiovascular disease mortality RR=1.26 (0.99,1.61)
- Total mortality RR=1.17 (1.03,1.33)

*(Omenn et al, 1996, NEJM)*

## Physicians Health Study

- 22,071 male U.S. physicians, ages 40-84; 12 years follow-up
- 50mg BC supplementation on alternate days
- 11% current smokers, 39% former smokers
- No difference in cancer incidence, cardiovascular disease incidence, or total mortality
- Lung cancer (82 - BC group, 88 - placebo group)

*(Hennekens et al, 1996, NEJM)*

## Risks and Benefits of Hormone Therapy

- Many observational studies and meta analyses reporting a 40-50% reduction in coronary heart disease, a duration-dependent 20-30% increase in breast cancer, reductions in fracture rates, an increase in venous thromboembolic disease, and a reduction in total mortality.

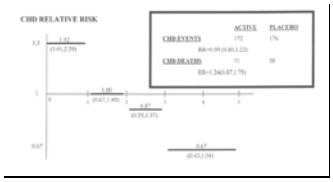
  e.g., Grodstein et al (1997, NEJM)…."After adjustment for confounding variables, current hormone users had a lower risk of death [RR=0.63 (0.56,0.70)]….Current hormone users with coronary risk factors had the largest reduction in mortality [RR=0.51 (0.45,0.57)]

- Postmenopausal estrogen/progestin intervention trial (1995, JAMA)...

  "Increase in HDL-C and decrease in LDL-C for each of several HRT preparations versus placebo (also coagulation factors, blood pressure, insulin, endometrial histology, bone mineral density,…)"

## Heart and Estrogen/Progestin Replacement Study

- 2,763 postmenopausal women with established coronary disease
- .625mg/day CEE plus 2.5mg/day MPA
- 11% lower LDL-C and 10% higher HDL-C in active versus placebo group
- No difference in CHD events over 4.1 year average follow-up




*(HERS, 1998, JAMA)*

## Editorials Following HERS

"EXPERIMENTATION TRUMPS OBSERVATION"

(Diana Petitti, 1998, JAMA)

'These findings are a sobering reminder of the limitations of observational research, the incompleteness of current understanding of the mechanisms of vascular disease and the dangers of extrapolation.'

'Compliance bias is large enough to explain entirely reductions in the relative risk of CHD between users and non-users of ERT and HRT of the magnitude found in observational studies.'

'The lipid hypothesis has dominated thinking about CHD for at least 4 decades. There is a growing recognition that thrombotic phenomena play an important role in acute coronary syndromes.'

'When an exposure can be assigned at random, it should be assigned randomly. Commitment to randomized trials as the standard of proof must be especially strong when the public health implications are so great.'

# Editorials Following HERS

"HERS -- A MISSED OPPORTUNITY"

(Malcolm Whitehead and Meir Stampfer, 1998, Climacteric)

- One preparation only. Only among women with established coronary heart disease.
- Failure of HERS to achieve the planned period of observation (4.1 vs. 4.75 years) is a 'major flaw'.
- 'There are other problems with HERS.' (Adherence rates vs. projected)
- 'Preliminary data from NHS support a pattern of early transient increase followed by a substantial decline in risk as the duration of therapy is extended. Thus, the results of HERS do not contradict the directly relevant observational data.'
- 'Unless prospective, randomized trials possess sufficient power then definitive conclusions cannot be drawn and more questions than answers will be the result. This, regrettably, is the HERS legacy.'

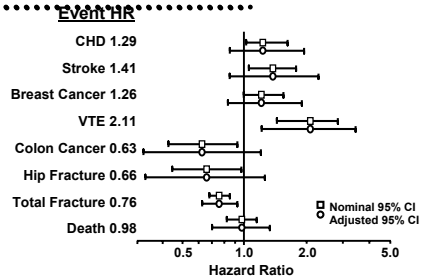
# Editorials Following HERS

"HRT AND THE HERS FINDINGS -- HAS THE GROUND SHIFTED?"

(Wulf Utian, 1998, Menopause Management)

- 'Unfortunately HERS was poorly conceived and designed, taking an unnecessary gamble that has now come back to haunt all parties concerned, and confuse consumers and providers alike.'
- '…already indications that progestins might attenuate some of the estrogen-induced cardiac-benefit effect. HERS would therefore have best included an estrogen-only arm, or have been designed as an estrogen versus placebo comparative study.'
- 'The initial negative effect is almost certainly due to the attenuation of estrogen-induced increase in coronary flow.'

# WHI: Results With CEE/MPA




**Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-33.**

## Sources of Primary Prevention Hypotheses / Interventions

1. Therapeutic research (and underlying basic sciences research)
2. Post-marketing epidemiologic surveillance of drugs, supplements, botanicals, …
3. Observational study of lifestyle factors and related intermediate outcomes

## Sources of Prevention Hypotheses

1. **Therapeutic research**

   Products that are effective for treating a chronic disease may also be effective in preventing the disease (e.g., tamoxifen, statins, alendronate).

   * Valuable source of interventions for persons at high risk of targeted diseases, but application may be late in pathogenesis process, and unlikely to lead to lifestyle recommendations that can improve overall health.
   * The 'biomonitor and treat' approach advocated by some seems inadequate for addressing current health issues (e.g., obesity epidemic).

## Sources of Prevention Hypotheses

2. **Post-marketing epidemiologic surveillance of drugs, nutritional supplements, botanicals, ...**

   Agents marketed under a particular indication or health claim may be associated with other health outcomes {e.g., HT (CHD, dementia), raloxifene (breast cancer), folic acid (CHD), aspirin (CHD)}.

   * Use of potent marketed products by major segments of the general population may imply a societal obligation to assess benefits versus risks.
   * Pharmacoepidemiology is complicated by confounding concerns as many biobehavioral factors may distinguish users of specific agents from non-users, and may distinguish long-term users from short-term users.

## Sources of Prevention Hypotheses

3. **Observational study of lifestyle factors in relation to chronic disease incidence (e.g., Nutrition and Physical Activity)**
   * Extensive observational study (ecologic, case-control, cohort) of nutrient consumption patterns, and considerable observational study of physical activity patterns, in relation to chronic disease risk. Also much study of these lifestyle factors in relation to intermediate outcomes (body mass and shape, blood lipids, …) and of intermediate outcomes in relation to disease risk.

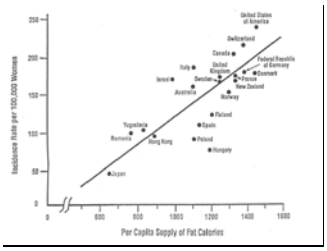
## Sources of Prevention Hypotheses

But….

* Human diet is a complex mixture of foods and nutrients with many highly correlated elements.
* Nutrient intakes may not be highly variable within populations available for study.
* Ability to assess (via self-report) short and long-term nutrient consumption, and short and long-term physical activity patterns limited by random and systematic measurement error issues; objective markers generally lacking.

- **Hence, reliability/interpretation of these observational associations often unclear (e.g., dietary fat and menopausal breast cancer).**

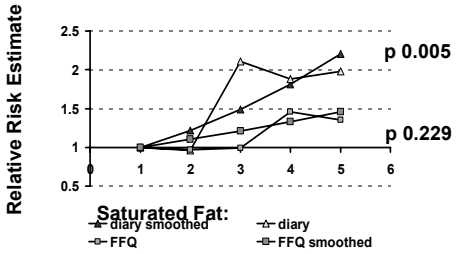
**Age-Adjusted Breast Cancer Incidence among Women of ages 55-69 in 1980 versus per capita for consumption in 1975**



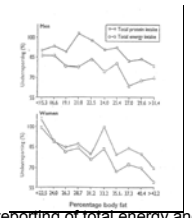
# Dietary Fat and Postmenopausal Breast Cancer

| | Fat Intake Quintile | | | | |
|---|---|---|---|---|---|
| **Case-control Studies** | | | | | |
| • Howe et al (1990) | 1 | 1.20 | 1.24 | 1.24 | 1.46(p<0.0001) |
| **Cohort Studies** | | | | | |
| • Hunter et al (1996) | 1 | 1.01 | 1.12 | 1.07 | 1.05 (p = 0.21) |

**Relative risks for breast cancer by quintile of saturated fat intake according to two different methods of assessing food consumption**




# Underreporting of Energy and Protein



Percentage underreporting of total energy and protein estimated from reported dietary intake and calculated urinary nitrogen output/24-hour energy expenditure as a function of percentage body fat, age, and smoking

*(Heitmann and Lissner, 1995, BMJ)*

## Prevention Intervention Development Needs

Context:

- Because of cost and logistics only a few interventions having substantive public health potential can be tested in full-scale trials with disease outcomes (health benefits vs. risks). Any such trial must be preceded by careful development work, including feasibility and intermediate outcome trials.
- An organized approach by the research community is needed to identify the interventions most worthy of testing in RCT's. We are somewhat better prepared for pharmaceutical interventions than for lifestyle interventions.
- The population science community needs to develop unity concerning the research strategies and methods needed to obtain reliable chronic disease prevention information.

## Prevention Intervention Development Needs

Specific needs include:

- ⑤ Methodologic research to enhance the reliability of observational studies of pharmaceutical products (e.g., w.r.t. confounding, adherence bias), or of lifestyle factors (e.g., objective markers of nutrient consumption)
- ⑤ Timely introduction of comprehensive intermediate outcome clinical trials when potential preventive agents become widely used (e.g., HT, aspirin, Cox 2 inhibitors, SERMs, testosterone)
- ⑤ A substantial basic science discovery research effort aimed at the identification and initial testing of chemopreventive and lifestyle modification interventions, perhaps using genomic and proteomic approaches.

## Prevention Intervention Development Needs

Specific needs (continued):

- ⑤ An enhanced lab-based program in human feeding trials and exercise intervention trials with a broad range of clinical and biological outcomes
- ⑤ An organized approach nationally to identify the chemopreventive and lifestyle interventions ready for testing, and appropriate funding levels and mechanisms..

## Summary

- Chronic disease population research is challenging, but has great public health potential
- An enhanced interdisciplinary hypothesis generation / **intervention development** enterprise is needed. RCT's having comprehensive intermediate outcomes can be expected to play a key role in the development and initial testing of preventive interventions.
- **Observational studies** will often play a key role in the further evaluation of prevention concepts. Strengthening of the methods for such studies may be needed in some contexts.
- **Randomized controlled intervention trials**, when practical, will provide the most reliable information, and should be conducted when the public health implications are sufficiently great.